The problems are shown as follows: The first is chronic poisoning due to long term administration, the second is the appearance of an HIV virus resistant to the medicine during the therapy, the third is the appearance of malignant tumors in prolongation of the HIV patient's life, the fourth is that the recovery of the immune system can not be monitored, the fifth is that there is not a method to monitor treatment effect, etc. Since such chemotherapy is not basic therapy for HIV infections, most people anticipate the development of a vaccine.

C4

Page 3, replace the paragraph beginning at line 20 with the following paragraph:

In this way, aiming at the development of an HIV treatment medicine, research to produce a vaccine and neutralizing antibody is flourishing, but useful medicine has not yet been developed.

C5

Page 4, line 9, replace the heading with the following new heading:

C6

SUMMARY OF THE INVENTION

line 21, replace the heading with the following new heading:

C7

DESCRIPTION OF THE PREFERRED EMBODIMENTS

replace the paragraph beginning at line 23 with the following paragraph:

The No.1 peptide in this invention that could solve the above subject;

A peptide having an affinity to gp120 represented by formula (1):

H-Al-A2-A3-A4-A5-R (SEQ ID No. 1),

(in the formula,

C8 Contd.

H means hydrogen,

A1 is aspartic acid, lysine, valine, glutamic acid, glycine, asparagine, or tyrosine residue,

A2 is valine, aspartic acid, tryptophan, lysine, phenylalanine, isoleucine, leucine, or tyrosine residue,

A3 is lysine, valine, aspartic acid, arginine, alanine, or tryptophan residue,

A4 is alanine, tryptophan, or glycine residue

A5 is glycine, alanine, valine, leucine, isoleucine, serine, threonine, methionine, asparagine, glutamine, histidine, lysine, arginine, phenylalanine, tryptophan, proline, or tyrosine residue,

R is OH derived from carboxyl group or NH_2 derived from acid amide group).

Page 5, replace the paragraph beginning at line 17 with the following paragraph:

Accordingly, the No. 1 peptide in this invention is a 5 amino acid sequence that was constituted by A1, A2, A3, A4 and A5 as described above, and all of the peptide including such amino acid sequences contained by the range of this invention. Thus, a peptide having an affinity to gp120 represented by

Formula (2): A1'-A2-A3-A4-A5-R-(SEQ ID No. 2),

(in the formula,

A1' means aspartic acid, lysine, valine, glutamic acid, glycine, asparagine, or tyrosine residue, or polypeptide residue that an arbitrary amino acid stood in line in the N-terminal side from this amino acid, A2, A3, A4, A5 and R have the same meaning as above)

or

~~Formula (3): H-A1-A2-A3-A4-A5-R-(SEQ ID No. 3),~~

~~(in the formula,~~

Sub. D'

C 9 cont'd

A5' means glycine, alanine, valine, leucine, isoleucine, threonine, methionine, asparagine, glutamine, histidine, lysine, arginine, phenylalanine, tryptophan, proline, or tyrosine residue, or polypeptide residue that an arbitrary amino acid stood in line in the C-terminal side of this amino acid, H, Al, A2, A3, A4 and R have the same meaning as the above) is entirely one aspect of the present invention.

Page 6, replace the paragraph beginning at line 14 with the following paragraph:

Then, the No. 2 peptide that could solve the above subject is;

a peptide having an affinity to gp120 represented by

Formula (4): H-a1-a2-a3-a4-a5-R (SEQ ID No. 4),

(In the formula,

H means hydrogen,

a1 is tyrosine, arginine, phenylalanine, glycine, tryptophan, histidine, or aspartic acid residue,

C 10 cont'd.

a2 is arginine, tyrosine, tryptophan, alanine, valine, glutamine, histidine, or lysine residue,

a3 is lysine, tyrosine, arginine, glutamic acid, methionine, or tryptophan residue,

a4 is glycine, alanine, valine, leucine, isoleucine, serine, threonine, methionine, asparagine, glutamine, histidine, lysine, arginine, phenylalanine, or tryptophan residue

a5 is glycine, alanine, valine, leucine, isoleucine, serine, threonine, methionine, asparagine, glutamine, histidine, lysine, arginine, phenylalanine, tyrosine, or tryptophan residue,

C 10 cancld.

R is OH derived from carboxyl group or NH_2 derived from acid amide group).

Page 7, replace the paragraph beginning at line 11 with the following paragraph:

Accordingly, the No.2 peptide in this invention is a 5 amino acid sequence that was constituted by a1, a2, a3, a4 and a5 as described above, and all of the peptide including such amino acid sequences contained by the range of this invention. Thus, a peptide having an affinity to gp120 represented by

Formula (5): a1'-a2-a3-a4-a5-R (SEQ ID No. 5),

(In the formula,

a1' means tyrosine, arginine, phenylalanine, glycine, tryptophan, histidine, or aspartic acid residue, or polypeptide residue that an arbitrary amino acid stood in the N-terminal side from this amino acid, a2, a3, a4, a5 and R have the same meaning as above.)

C 11

or

Formula (6): H-al-a2-a3-a4-a5' (SEQ ID No. 6),

(In the formula,

a5' is glycine, alanine, valine, leucine, isoleucine, serine, threonine, methionine, asparagine, glutamine, histidine, lysine, arginine, phenylalanine, tyrosine, or tryptophan residue, or polypeptide residue that an arbitrary amino acid stood in line in the C-terminal side of this amino acid, H, a1, a2, a3, and a4 have the same meaning as above)

is entirely one aspect of the present invention.

Page 8, replace the paragraph beginning at line 18 with the following paragraph:

However, the above mentioned "peptide" that is used in this invention contained in the C-terminal peptide is COOH, acid amide and ester etc., and particularly, so long as we do not specify, it contains an amino acid number (oligopeptide) of less than 10, or a polypeptide of more than this.

C 12

replace the paragraph beginning at line 22 with the following paragraph:

An amino acid in the above mentioned peptide contains the derivatives that are protected by the protecting functional group. As such amino acid derivatives, it is marked by substitution or modification without exchanging the peptide structure; exchanging the length of the carbon chain etc., or the protecting amino acid derivatives corresponding to various amino acids, but all of these various amino acids can be used in this invention. For example, as tyrosine derivatives, there is 2,6-dichloro-L-tyrosine having chloride in the side chain, p-Nitro-L-phenylalanine that hydroxyl group of p-side in phenylalanine was substituted Nitroyl group, and 4-chloro-L-phenylalanine that the hydroxyl group was substituted chloride, etc. In addition, as valine derivatives, there are Norvaline: N-α-L-norvaline, or MeVal: N-α-L-valine, etc.

C 13

Page 9, replace the paragraph beginning at line 9 with the following paragraph:

The reason that conventional medicine, such as a vaccine or neutralizing antibody can not be used clinically is that the HIV region the body can recognize as antigen is the V (hypervariable region) region in the envelop gp120, and this is the most problematic. So, the inventors researched a peptide which had a specific infinity to gp120, and as a result, developed a superior peptide and have already applied for a patent (Japanese Patent Application No. H 8-351474 and Japanese Patent Application No. H 8-351475). They developed a peptide which has a high specific affinity to gp120, of the same affinity or more compared to antibody, and which is

C 14 cont'd.

C14 concld.
additionally resistant to heat with a high pressure, such as in autoclave treatment.

Page 10, replace the paragraph beginning at line 2 with the following paragraph:

The peptide in this invention is constituted as mentioned above and is fundamentally shown as 5 amino acid residues which appear in;

C15

①formula (1): H-A1-A2-A3-A4-A5-R (SEQ ID No. 1),

(in formula, A1, A2, A3, A4, A5 and R, the meanings are the same as before)

or,

②formula (4): H-a1-a2-a3-a4-a5-R (SEQ ID No. 4),

(in formula, a1, a2, a3, a4, a5 and R, the meanings are the same as before).

replace the paragraph beginning at line 10 with the following paragraph:

This peptide has a molecule separate in each and is not (or in peptide), the amino acid sequence mentioned above ①peptide,

formula (2): A1'-A2-A3-A4-A5 (SEQ ID No. 2); or

formula (3): Al-A2-A3-A4-A5' (SEQ ID No. 3)

or above-mentioned ②peptide includes the sequence which lined up from N-terminus.

C16 contd.

Formula (4): a1'-a2-a3-a4-a5 (SEQ ID No. 5); or

Formula (5): a1-a2-a3-a4-a5' (SEQ ID No. 6)

(in formula, A1', A2, A3, A4, A5', a1'a2, a3, a4, a5', the meanings are the same as before).

Sub D2

Of course, in A1'-A2'- A3'- A4'-A5' (SEQ ID Nos. 1-3) or a1'-a2'-a3'-a4'a5' (SEQ ID Nos. 4-6), there includes peptides which lined up repeatedly by this order. In brief, this invention

C 16 concld.

~~includes all of the peptides which consist of 5 amino acid residues and have an affinity to gp-120~~

sub. D2

replace the paragraph beginning at line 22 with the following paragraph:

The peptide in this invention can be synthesized by conventional methods; For example, the first of this invention is constituted from A1-A2-A3-A4-A5 (SEQ ID No. 1), is synthesized and the A5 glycine residue, carboxyl of N-protective glycine is bound to some carrier, such as insoluble resin, which has a functional group that can couple to carboxyl. After this, the protected amino acid in each, from A2 to A5, is bound in order by a solid phase synthetic method, and the peptide shown in this invention can be obtained by reacting the above mentioned insoluble resin and eliminating the protection of the amino acid.

C 17

Page 12, replace the paragraph beginning at line 7 with the following paragraph:

Moreover, "protecting amino acid" in the case of the above means protected amino acid with protecting group by conventional method. To synthesize the peptide invented, it is pleasing to use either of the protecting groups shown in the following examples.

C 18

Page 14, replace the paragraph beginning at line 7 with the following paragraph:

The peptide that is obtained in this way can be purified by various methods; chromatography (gel, ion-exchange, hydrophobicity, adsorption, reverse phase), electrophoresis and ultrafiltration.

C 19

replace the paragraph beginning at line 10 with the following paragraph:

Also included in this invention is a peptide that was substituted on a similar protein(active center or binding domain of antibody, receptor, enzyme and etc.) by a gene recombination method in the case of above peptide. For example, if we produce human anti-gp120 antibody by gene recombinant method, we produce the above-mentioned peptide which is

C 20 cont'd.

based on the U.S. Patent No. 114632. Namely, this peptide is transduced amino acids of hypervariable cluster in CDR (complementary determination region, VH31 to VH35)-1 and CDR-2(VH50 to 52, and/or VH58 to 60), which relates recognition of epitope during the V region in the human immunoglobin gene (Ohno, S., Mori, N. & Matunaga, T.; Proc. Natl. Acad. Sci. USA. 82, 2945, 1985).

Page 16, below Table 1, insert the following:

Nos. 1-19 and 22-27 of Table 1 correspond to SEQ ID No. 1.

No. 20 of Table 1 corresponds to SEQ ID No. 7.

No. 21 of Table 1 corresponds to SEQ ID No. 8.

below Table 2, insert the following:

Nos. 28-40 of Table 2 correspond to SEQ ID No. 1.

Replace pages 17, 18 and 19 of the specification with the attached substitute pages 17, 18 and 19.

Page 20, replace the paragraph beginning at line 19 with the following paragraph;

It is selected voluntarily among the inside of linear, branched and cyclic, as polymer in case of above. For example, it can be used as an insoluble solid phase carrier of amino acidic homopolymer of polylysine and polyglutamic acids, or cyclic polyamine, cyclodextrin, cyclic peptide and then polystylene, polypropyrene, nylon, silica-gel, polyethyleneglycol, cellulose, polyacrylamide, and others.

Page 21, replace the paragraph beginning at line 18 with the following paragraph:

Moreover, for binding cyclic polymer of cyclic polyamine, cyclodextrin, and cyclic peptides, it is possible to synthesize directly and make the peptide of upper expression from the

same functional group, or to bind directly/indirectly to a new synthetic peptide separately or to a functional group of the cyclic polymer. Then, to bind the insoluble carrier of silica gel etc., after it is introduced to the same functional group carrier in advance, it can be synthesized and just grow directly peptide of upper expression from the functional group, or conjugate directly/indirectly from the functional group of insoluble carrier to the new synthetic peptide separately. In addition, the particular size and shape of the carrier having this same functional group is not limited, and selection and utilization of: spherical, hollow fibrous, fibrous shapes can be made according to their purpose and then, it is not limited at all by size and shape and can be introduced to several functional groups.

C23 Corrected

Page 22, replace the paragraph beginning at line 14 with the following paragraph:

The size of linear polymer in these can be appropriately selected, according to the purpose of use, and includes some monomer of around 3 that does not usually seems to be recognized as a polymer, but is not limited at all by the size or number of functional groups. For binding a peptide or upper expression to this linear polymer, you may directly synthesize and just grow it from the same functional group, or may directly/indirectly conjugate a new synthetic peptide separately to the functional group of the linear polymer.

C24

Page 25, replace the paragraph beginning at line 17 with the following paragraph:

Branched polymer binding compound was synthesized by extending No.12 peptide on the above Table 3 from N-end amino acid MAPs (Multiple antigenic peptide). After the compound was suspended in phosphate buffer, it was purified through gel chromatography and affinity chromatography by gp120 conjugated carrier, and we synthesized branched polymer binding compound to the peptide in this invention (2).

C25

Page 29, below Table 5, insert the following:

C26 Nos. 1-7 of Table 5 correspond to SEQ ID No. 1.

Page 30, below Table 6, insert the following:

C27 Nos. 1-19 of Table 6 correspond to SEQ ID No. 4.

Page 32, below Table 7, insert the following:

Nos. 1-15 and 18-26 of Table 7 correspond to SEQ ID No. 1.

C28 No. 16 of Table 7 corresponds to SEQ ID No. 7.

No. 17 of Table 7 corresponds to SEQ ID No. 8.

below Table 8, insert the following:

Nos. 27-36 of Table 8 correspond to SEQ ID No. 1.

Page 33, below Table 9, insert the following:

Nos. 1-12, 14-17, 19 and 21-26 of Table 9 correspond to SEQ ID No. 4.

C29 No. 13 of Table 9 corresponds to SEQ ID No. 9.

No. 18 of Table 9 corresponds to SEQ ID No. 10.

No. 20 of Table 9 corresponds to SEQ ID No. 11.

Replace page 34 of the specification with the attached substitute page 34.

Page 35, below Table 11, insert the following:

C30 No. 1 of Table 11 corresponds to SEQ ID No. 1.

No. 2 of Table 11 corresponds to SEQ ID No. 12.

No. 3 of Table 11 corresponds to SEQ ID No. 13.

replace the paragraph below Table 11 with the following paragraph:

C31 cont'd. From Table 11, both No.3 with only 3 amino acids (there are no A4 and A5 amino

acids) and in No.2 with only 4 amino acids(there are no A5 amino acids) neutralizing activity decreased remarkably compared to No.1 with five amino acids. Namely, by the amino acid numerical decrease, the neutralizing activity has a tendency to fall, and particularly No.3, having only three amino acids.

replace the paragraph beginning at line 2 from the bottom with the following paragraph:

To examine the effect of a4 and a5 amino acids on neutralizing activity, the chain length of No.8 in Table 9 were changed. The activity was measured the same as in example 1. Their results are shown in Table 12. Face note, NE means "NO EFFECT".

Replace page 36 of the specification with the attached substitute page 36.

Page 37, below Table 13, insert the following:

Nos. 1-2 of Table 13 correspond to SEQ ID No. 4.

No. 3 of Table 13 corresponds to SEQ ID No. 16.

replace the heading and paragraph beginning at line 11 from the bottom with the following heading and paragraph:

EXAMPLE 6: Effect of A4 and A5

in this invention on agglutinin

We examined the effect of A4 and A5 on agglutinin test as shown in TABLE 14. The No.1 peptide was used as a positive control, while we used a peptide (No.2) that kind of A4 amino acids was changed to leucine, hydrophobic amino acid of same as alanine, or a peptide(No.3) that was changed to aspartic acid, acidic amino acid; similarly, the peptide(No.4) was changed to proline, and the peptide(No.5) was changed to glutamic acid. Then, we examined

the effects on neutralizing activity the same as in EXAMPLE 2. The results are shown jointly in Table 14. Face note, ± means "an agglutinin in trace degree".

Page 38, below Table 14, insert the following:

Nos. 1 and 4 of Table 14 correspond to SEQ ID No. 1.

No. 2 of Table 14 corresponds to SEQ ID No. 17.

No. 3 of Table 14 corresponds to SEQ ID No. 18.

No. 5 of Table 14 corresponds to SEQ ID No. 19.

Page 40, replace the paragraph beginning at line 3 with the following paragraph:

The peptide bound to Sephadex 6MB that was prepared in SYNTHESIS 7 was added to the various kinds of density prepared horseradish peroxidase (HRP) labeled HIV-1-gp120(Immuno Diagnosis Co.) and enzyme unlabeled HIV-1-gp120 previously in each and constant disassociation(kd) of peptide in this invention calculated by drawing up A Schacherd Plot we calculated was kd = 2.14×10^{-10}M.

Page 46, line 16, delete the entire heading.

Please replace the Sequence Listing of record pages 1-8 with the attached substitute Sequence Listing consisting of pages 1-8.

In the Abstract:

Page 51, line 1 replace the heading with the following new heading:

ABSTRACT OF THE DISCLOSURE

replace the paragraph beginning at line 3 with the following paragraph: